REMARKS

Upon entry of this amendment, claims 1, 10-13, 15, 29-30, 33-50 are pending in the instant application. To expedite the prosecution of the instant application, claim 31 has been cancelled herein, and Applicant reserves the right to prosecute that subject matter, as well as the originally presented claims, in later applications. Claims 1, 29, and 33-36 have been amended, and claims 43-50 have been added. The present amendments are fully supported by the specification and the claims as originally filed. For example, support for new claims 43-47 can be found in the specification at least at page 6, lines 4-5; page 11, lines 9-10; and page 21, lines 12-28. Support for the methods recited by new claims 48-50 can be found in the specification at least at page 36, lines 16-24 and at page 20, lines 5-6. Accordingly, no new matter has been added by the amendments made herein.

Applicant notes that claims 37-42 have been allowed, and claims 1, 10-13, 15, 29 and 33-36 have been found to be "free of the art of record."

Specification

Applicant notes that the Examiner has withdrawn all objections to the specification. The Examiner has also acknowledged that this application complies with the requirements set forth in 37 C.F.R. §§ 1.821-825.

Claim Objections

Applicant notes that the Examiner has withdrawn his objection to claims 1 and 29 as "[a]mendments to the claims has obviated the basis of the objection." (Office Action, page 2).

Claim Rejections Under 35 USC § 112

Rejections Under 35 USC § 112, First Paragraph

Claims 1, 10-13, 15, 29 and 31 stand rejected under 35 USC 112, first paragraph, for lack of enablement. According to the Examiner:

> [W]ith respect to the method practiced *in vivo*, only the use of adenoviral particles comprising the adenovirus vector comprising a CMV promoter operably linked to a polynucleotide sequence encoding PDX-1 would be enabled for the delivery by various routes of administration. ...The polynucleotide of an adenovirus themselves lack the ability to specifically target the liver and it is only

in the context of the polynucleotide in a adenoviral particle which would be enabled for any route of delivery. (Office Action, pp. 4-5).

Applicant traverses this rejection. Independent claim 1 (and its dependent claims) has been amended as suggested by the Examiner to recite a method of inducing the expression of a pancreatic hormone selected from the group consisting of insulin, somatostatin, and glucagon in the liver of a mammal, wherein the method includes the step of administering to the mammal *an adenoviral particle comprising an adenovirus vector* that includes a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount sufficient to induce said pancreatic hormone expression in said liver in said mammal.

Similarly, independent claim 29 (and its dependent claim) has been amended to recite a method of inducing a pancreatic islet gene expression profile in a liver cell of a subject. The method according to claim 29 comprises the step of administering to the subject *an adenoviral particle comprising an adenovirus vector* that includes a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount sufficient to induce said pancreatic islet gene expression in said liver cell in said subject.

Likewise, claims 33-36 have been amended herein to recited methods of inducing the expression of insulin, somatostatin, glucagon, or prohormone convertase 1/3 (PC 1/3) in the liver of a mammal by administering to the mammal *an adenoviral particle comprising an adenovirus vector* that includes a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount sufficient to induce said selected expression in said liver of said mammal.

Thus, pending claims 1-36, as amended herein, recite *an adenoviral particle that comprises an adenovirus vector*, as suggested by the Examiner at pages 4-5 of the Office Action. The Examiner has acknowledged that these claims are enabled. At page 4, lines 13-16 of the Office Action, the Examiner explicitly states that the present specification is enabling for "the use of adenoviral particles comprising the adenovirus vector comprising a CMV promoter operably linked to a polynucleotide sequence encoding PDX-1 would be enabled for the delivery by various routes of administration." Moreover, at page 5, lines 9-10, the Examiner also asserts that an adenovirus vector would be enabled "for any route of delivery" "in the context of the

polynucleotide in a adenoviral particle." Accordingly, claims 1-36 are enabled by the instant specification, and this rejection should be withdrawn.

Claim 31 has been cancelled herein. Thus, this rejection has been rendered moot and should be withdrawn.

New claims 43-47 are directed to methods of inducing pancreatic hormone expression in a skin *cell* by introducing the cell to a composition that includes an adenovirus vector having a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide. The pancreatic hormone expressed is insulin, somatostatin, glucagon or prohormone convertase 1/3 (PC 1/3).

New claims 48-50 are directed to methods of inducing endogenous PDX-1 expression in a *cell* by introducing the cell to a composition that includes an adenovirus vector having a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, thereby inducing endogenous PDX-1 expression in the cell.

Thus, these new claims are directed to methods relating to gene expression in a *cell*. The Examiner has acknowledged that "methods restricted to administration of an adenovirus vector" by contacting a *cell* with the adenovirus vector are "fully enabled because the vector is delivered directly to the cell." (Office Action, p. 4). As claims 43-50 are directed to methods of administering a vector by delivering the vector directly to a cell, these claimed methods are enabled.

In addition, Applicant submits herewith a Declaration Under 37 C.F.R. §1.132 of Dr. Sarah Ferber, the named inventor of the present application, which demonstrates that new claims 43-50 are enabled by the specification as filed in the instant application. As described above, new claims 43-47 are directed to methods of inducing pancreatic hormone production in a skin cell. The studies presented in this Declaration demonstrate that AD-CMV-PDX-1 can be used in the transdifferentiation of skin cells (*i.e.*, keratinocytes). (*See* Ferber Decl., ¶ 5-8, Appendix). Four different treatment groups of keratinocytes were used to show insulin, glucagon and somatostatin gene expression in keratinocytes treated with AD-CMV-PDX. (*See* Ferber Decl., ¶ 6-8, Appendix). In these studies, ectopic expression of PDX-1 induced skin cell transdifferentiation. (*See* Ferber Decl., ¶ 6-8). Accordingly, the methods of the instant application can be used in the transdifferentiation of a skin cell, as well as in the transdifferentiation of a liver cell.

Moreover, the specification provides the necessary guidance to extend the methods of the instant application to skin cells. One of ordinary skill in the art at the time the instant application, with the specification in hand, would know how to make and use the methods of the instant invention without undue experimentation. (*See* Ferber Decl., ¶ 9). Accordingly, new claims 43-47 are enabled by the specification as filed, and Applicant requests that the Examiner allow these new claims.

In addition, the Declaration of Dr. Ferber demonstrates that new claims 48-50 are enabled by the specification as filed in the instant application. As described above, new claims 48-50 are directed to methods of inducing endogenous PDX-1 expression in a cell by introducing the cell to a composition that includes an adenovirus vector having a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, thereby inducing endogenous PDX-1 expression in the cell.

The studies presented in this Declaration demonstrate that delivery of an adenovirus vector, such as, for example, AD-CMV-PDX-1, induces auto-induction of endogenous, but otherwise silent genes, such as, for example, PDX-1. (*See* Ferber Decl., ¶ 11-14, Appendix). Specific oligonucleotide primers were used to distinguish between ectopic PDX-1 transgene mRNA (rat) and endogenous mRNA (mouse). Endogenous PDX-1 expression in treated livers throughout the duration of the experiment was found to be exclusive to mice that had received the rat PDX-1 transgene. (*See* Ferber Decl., ¶ 12, Appendix). In these studies, ectopic expression of PDX-1 induced endogenous expression of mouse PDX-1 at substantial levels throughout the whole duration of the experiment. (*See* Ferber Decl., ¶ 12-13). Accordingly, the methods of the instant application can be used in the auto-induction of endogenous, but otherwise silent genes in a cell, such as, for example, PDX-1.

Moreover, the specification provides the necessary guidance to extend the methods of the instant application to the auto-induction of endogenous, but otherwise silent genes in a cell. One of ordinary skill in the art at the time the instant application, with the specification in hand, would know how to make and use the methods of the instant invention without undue experimentation. (*See* Ferber Decl., ¶ 15). Accordingly, new claims 48-50 are enabled by the specification as filed, and Applicant requests that the Examiner allow these new claims.

Rejections Under 35 USC § 112, Second Paragraph

Claim 31 stands rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner has asserted that "the claim is vague and unclear in the recitation of 'in amount effective to induce pancreatic hormone expression in the liver cell' because the polynucleotide does not induce the expression in the cell, it is the PDX-1 protein encoded and produced by the polynucleotide."

Claim 31 has been cancelled herein. Accordingly, this rejection has been rendered moot and should be withdrawn.

Claim Rejections Under 35 USC § 102

Rejection of Claim 31 Under 35 USC § 102(b) in view of Milewski

Claim 31 has been rejected under 35 USC 102(b) as being anticipated by the teachings of Milewski *et al.*, 139(3) Endocrinology 1440-49 (1998) ("Milewski"). In particular, the Examiner asserts that "the limitation of 'an amount effective to induce pancreatic hormone expression in a liver cell' describes an inherent property of PDX-1 protein and provides only an intended use of the polynucleotide." (Office Action at pp. 7-8).

As noted above, claim 31 has been cancelled herein. Accordingly, this rejection has been rendered moot and should be withdrawn.

Applicant notes that at page 9 of the Office Action, the Examiner has acknowledged that Marshak does not anticipate claim 42.

Rejection of Claim 31 Under 35 USC § 102(b) in view of Marshak

Claim 31 also stands rejected under 35 USC §102(b), as being anticipated by Marshak *et al.*, 93 Proc. Natl. Acad. Sci. U.S.A. 15057-62 (1996) ("Marshak"). According to the Examiner, "the limitation of 'an amount effective to induce pancreatic hormone expression in a liver cell' describes an inherent property of PDX-1 protein and provides only an intended use of the polynucleotide." (Office Action at pp. 9).

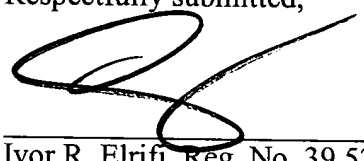
Again, claim 31 has been cancelled herein. Accordingly, this rejection has been rendered moot and should be withdrawn.

Applicant also notes that at page 9 of the Office Action, the Examiner has acknowledged that Marshak does not anticipate claim 42.

CONCLUSION

On the basis of the foregoing amendments and arguments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529
Cynthia Kozakiewicz, Reg. No. 42,764
MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY and POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241